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## REMARKS

Claims 1-8 remain in the application. Claims 1-3 and 6-8 are in independent form.

In order to further prosecution, the claims have been amended to more specifically recite the nitric oxide donors that can be used to promote new neuron growth. Support for the nitric oxide donors can be found in the specification as originally filed at page 5, lines 1-10, wherein there are specifically disclosed examples of nitric oxide donors that are capable of promoting new neuron growth.

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Moskowitz patent. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by the Moskowitz patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Office Action states that the Moskowitz patent teaches a method of treating strokes and the resulting neurological damage by administering nitric oxide releasing compounds. The therapeutic target of the Moskowitz approach is the reduction of cerebral infarction (i.e. volume of dead brain tissue) after ischemic stroke that is stroke caused by a lack of blood flow to the brain. Moskowitz seeks to increase blood flow to the brain to limit volume of infarction. In other words, the patent discloses treating injured brain in an attempt to salvage brain tissue. The treatment disclosed in the

Moskowitz patent is limited to times early after onset of ischemic stroke when blood flow increase can reduce the volume of blood flowing to the damaged tissue. In the Moskowitz patent, there is disclosed that the reduction of the infarction is mediated by administration of a substrate for NO before or early (within the first 1-2 hours) after stroke. The substrate is given from 16 hours before stroke to 2 hours after stroke. This enhances blood flow to the brain and thereby counteracts some of the loss of blood flow initiated by the stroke. The Moskowitz patent states in column 1 line 31 that, "the nervous system lacks the ability to regenerate," in column 1 lines 40- 44, "the ultimate size of the infarct which forms the basis of medical therapy is the extent of vascular support." Thus, according to the Moskowitz patent, the intervention must be designed to improve blood flow and thereby to reduce the ischemic lesion, because when the lesion is complete, the lesion cannot be reduced by treatment there is no benefit.

The Moskowitz patent also discloses that the brain cannot regenerate. The data presented in the Moskowitz patent only relate to treatment of a model of ischemic stroke with a substrate of NO. All data presented by Moskowitz show a reduction of volume of cerebral infarction, dilation of blood vessels, and, as noted in column 3 line 18, the approach of the Moskowitz patent is to "limit the extent of stroke-associated infarct." The patent discloses that treatment should preferably begin shortly after the initiation of stroke and preferably at any point in time prior to the completion of the infarction process. There is disclosed that, "treatment may be initiated, however, at any point in time prior to the completion of the infarction process." The disclosure also provides that "in certain instances, the methods of the invention may be used to treat a patient after the completion of a stroke episode." There is no disclosure of what those "instances" are or how they relate to treatment and thus, the disclosure does not enable one of skill in the art to ascertain the possibility that any beneficial effects are afforded a patient who has the NO compound administered post-stroke. Further, there is no disclosure that treatment at any point subsequent to the completion of the stroke would function in the desired manner. It is commonly known to those of skill in the art that there is a distinct period of time in which the damage occurring from a stroke can be mediated. Subsequent to this time period, it was believed that treatment was futile.

Further, the Moskowitz patent and all other prior art disclosures disclose methods for limiting the infarction process or increasing the blood flow to the areas of the brain that were damaged by stroke. There is no disclosure for the regeneration of neurons as is disclosed in the presently pending independent claims.

In contradistinction, the presently pending independent claims claim NO donors, PDE5 inhibitors and related compounds, for inducing brain remodeling and restoring neurological function, completely independent of the effect of NO donors on the volume of infarction. As disclosed throughout the currently pending patent application and specifically claimed, the functional benefit is derived from treatment under conditions in which the volume of brain damage is unaltered by the treatment. Further, the claimed methods are used to treat and remodel viable brain. The method activates endogenous restorative mechanisms within the non-injured tissue, so as to compensate for the damage, and thereby to enhance neurological function. The therapy can be administered days and weeks after the injury, and the neurogenesis is totally independent of any affect of treatment of the lesion. The claimed method is specifically delayed until the completion of infarction, and can even be administered 24 or more hours after stroke. The method and compound of the presently pending independent claims claim inducing brain remodeling an event that is independent of the reduction of the volume of cerebral infarction. There is no connection or association of reduction of volume of cerebral infarction and with the production of new brain cells. There is no requirement of the presence of a NO donor to induce brain remodeling and functional benefit.

The Office Action has maintained that Applicants' definition of promoting neurogenesis includes proliferation of parenchymal cells and as such, is much broader than originally suggested. However, when read more specifically, the definition of promoting neurogenesis is defined as "new neuronal growth or enhanced growth of existing neurons, as well as growth and proliferation of parenchymal cells and cells that promote tissue plasticity." The recovery includes the increase of parenchymal cells as a result of the proliferation of new neurons, therefore, the parachymal cells are

increased as a result of the neurogenesis and thus, are an effect of neurogenesis. Additionally, the methodology disclosed in the Moskowitz patent does not initiate neurogenesis. In fact, the Moskowitz patent discloses that neurons cannot regenerate. It is actually contrary to the common knowledge of those in skill in the art to have administered any compounds after the completion of the stroke. Instead, it was believed by those of skill in the art that upon completion of the stroke, an individual was no longer able to be treated and must instead learn to survive with the results of the stroke. Since the Moskowitz patent does not disclose or suggest the method and compound of the presently pending independent claims, the claims are patentable over the Moskowitz patent, and reconsideration of the rejection is respectfully requested.

Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Bredt et al. reference. Reconsideration of the rejection under 35 U.S.C. §103(a) over the Bredt et al. reference, as applied to the claims is also respectfully requested.

It is Hornbook Law that before two or more references may be combined to negative patentability of a claimed invention, at least one of the references must teach or suggest the benefits to be obtained by the combination. This statement of law was first set forth in the landmark case of Ex parte McCullom, 204 O.G. 1346; 1914 C.D. 70. This decision was rendered by Assistant Commissioner Newton upon appeal from the Examiner-in-Chief and dealt with the matter of combination of references. Since then many courts have over the years affirmed this doctrine.

The applicable law was more recently restated by the Court of Appeals for the Federal Circuit in the case of ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572,1577, 221 U.S.P.Q. 929 (Fed. Cir. 1984). In this case the Court stated, on page 933, as follows:

> Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under Section 103 teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any

> such suggestion or incentive. Accordingly we hold that the court below erred as a matter of law in concluding that the claimed invention would have been obvious to one of ordinary skill in the art under section 103.

This Doctrine was even more recently reaffirmed by the CAFC in Ashland Oil, Inc. v. Delta Resins and Refractories, Inc., et al., 776 F.2d 281,297, 227 U.S.P.Q. 657,667. As stated, the District Court concluded:

> Obviousness, however, cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion, or incentive in this prior art which would have made such a combination appropriate.

The Court cited ACS Hospital Systems, Inc. in support of its ruling. This Doctrine was reaffirmed in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995).

The Office Action states that the Bredt et al. reference teaches that nitric oxide is a diffusible multifunctional second messenger that has been implicated in numerous physiological functions in mammals ranging from dilation of blood vessels to immune response and potentiation of synaptic transmission. However, when read more specifically, there is no disclosure in the Bredt et al. reference for the potentiation of synaptic transmission. What is disclosed is that nitric oxide influences neurotransmitter release. Data is described on page 185 showing that NOS inhibitors block the release of neurotransmitters. There is no disclosure that the potentiation of synaptic transmission is related to synaptogenesis. The effect of NO on the release of neurotransmitters is not associated in any way with synaptogenesis. Synaptogenesis is the formation of new synapses, new connections in the growth and extension of synaptic and dendritic structures. The structural change of neurons is unrelated to the potentiation of neurons to release chemicals associated in electrical communications (i.e., neurotransmitters). Thus, NO as a neurotransmitter or a modulator of neurotransmission is distinct from NO as a promoter of synaptogenesis and one function is not related to the other. Further, the fact that NO has been implicated in numerous physiological and pathophysiological

functions (i.e., cell death as extensively discussed on page 187-191 of the Bredt et al. reference) does not imply that NO is involved in brain plasticity and the production of new neurons, blood vessels, or synapses. There is no suggestion or teaching in the Bredt et al. reference of the ability of NO to induce functional improvement in brain plasticity after stoke or neural injury. Thus, the Bredt et al. reference does not disclose or suggest the invention as claimed in the presently pending independent claims, and as such the presently pending independent claims are patentable over the Bredt et al. reference and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. Claims have also been amended to clearly distinguish over the prior art. The application is made at least in better condition for appeal as the amendment removes many issues thereby simplifying the issues on appeal. Further, the claims have been amended to more specifically define the invention while raising no new issues that would require any further searching. Rather, the amendments have been made in view of comments made in the Office Action that clearly distinguish the presently pending claims over the cited prior art. Hence, it is respectfully requested that the amendment be entered.

This amendment could not have been made earlier as the amendment further defines the claims over the prior art in accordance with the suggestion made in the Office Action, the suggestion first being made in the outstanding Office Action. Hence,

since there remain no further issues to be resolved, it is respectfully requested that the present amendment be entered.

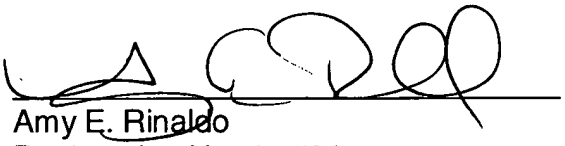
In conclusion, it is respectfully requested that the present amendment be entered in order to place the application in condition for allowance, which allowance is respectfully requested.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES, PLLC



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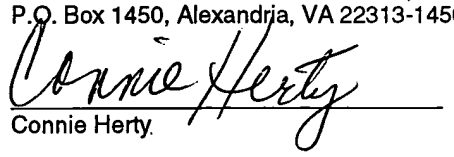

Connie Herty